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EXAMINER	
GARVEY, TARA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/642,322	RAUCY, JUDY	
	Examiner	Art Unit	
	Tara L Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the phrase "said reporter" is used on lines 10 and 13. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 recites the limitation "said enzyme involved in drug metabolism" in line 1. Claim 2 is dependent on claim 1, which does not recite the limitation of an "enzyme." There is insufficient antecedent basis for this limitation in the claim.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of the phrase "produces transcriptional activation of a gene encoding a protein involved in drug metabolism" is unclear because in the assay the gene encoding a protein involved in drug metabolism is not actually encoded by the expression plasmid, instead a regulatory region of the drug metabolism gene controls the expression of a reporter gene.

Claim Rejections - 35 USC § 102

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 9-11, 14-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Liddle et al (WO 99/61622).

Claim 1 is drawn to a cell that comprises one nucleic acid that containing a reporter gene and a promoter or enhancer element for a human or non-human protein involved in drug metabolism, which controls the expression of the reporter gene and a second nucleic acid that encodes a transcription factor or intracellular receptor. When the cell is treated with a compound, the reporter gene is expressed due to the interaction of protein with the regulatory element. Claim 2 limits the invention of claim 1 to various drug metabolism enzymes. Claims 3 and 6 limit the invention of claim1 to a

reporter gene that encodes an enzyme or detectable protein and is inserted into the chromosome. Claims 4 and 5 limit the invention of claim 1 to the first nucleic acid being extrachromosomal or within the chromosome. Claim 9 limits the invention of claim 1 to the intracellular receptor or transcription factor forming a complex with a compound and transcriptionally activating a gene encoding a protein involved in drug metabolism. Claim 10 limits the invention of claim 1 to an intracellular receptor or transcription factor that is an orphan receptor or a hormone receptor. Claim 11 limits the invention of claim 1 to the second nucleic acid being extrachromosomal. Claims 14-18 limit the invention of claim 1 to the cell type. Claim 19 is drawn to a method for evaluating compounds that induce the expression of protein involved in drug metabolism by contacting a test compound with a cell of claim 1, detecting the expression of the reporter gene as an indication that the compound altered the expression of a gene encoding a protein involved in drug metabolism.

Liddle et al teach a construct containing human CYP3A4 (a P450 enzyme involved in drug metabolism) regulatory elements such as PXRE and XREM and a reporter gene that can encode an enzyme such as luciferase or a detectable protein such as a green fluorescent protein (page 3 lines 21-31, page 4 lines 2-3, page 14 lines 30-35 and page 16 lines 3-10) and transfection of this construct either as an extrachromosomal element or by incorporation into the chromosome of any cell type (page 4 lines 21-23 and page 25 claim 25). In addition, they teach cotransfection of HepG2 liver cells with hPXR expression vector and the CYP3A4-XREM-reporter construct in the presence of various drugs to determine the effect of the compounds on

CYP3A4 gene transcription (page 6 lines 12-20 and page 16 lines 1-16). Thus, Liddle et al teach all that is recited in the instant claims.

Claims 1-4, 9-11 and 14-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Lehmann et al (Journal of Clinical Investigation, (1998), volume 102, issue 5, pages 1016-1023).

Claims 1-4, 9-11 and 14-19 have been described previously.

Lehmann et al teach transient transfection of CV-1 kidney cells with human and mouse PXR (pregnane X receptor which is an orphan hormone receptor) expression plasmids and a reporter plasmid containing a CYP3A4 PXRE regulatory element and a reporter gene such as the enzyme CAT, treatment of the transfected cell with various compounds and detection of reporter gene expression as an indication of the effect of the interaction of the compound and PXR on the regulation of CYP3A4 gene expression (page 1017, left column, second full paragraph, lines 15-18; page 1019, right column, second paragraph, lines 11-18 bridging page 1020, lines 1-3; page 1020, lines 1-15). CYP3A4 is a P450 enzyme involved in drug metabolism. Thus, Lehmann et al teach all that is recited in the instant claims.

Claims 1-6, 9 and 12-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Quattrochi et al (Molecular Pharmacology, 1993, volume 43, pages 504-508).

Claims 1-6, 9 and 12-19 have been described previously. Claims 12 and 13 limit the invention of claim 1 to the second nucleic acid being within the chromosome or endogenous to the cell.

Quattrochi et al teaches a human hepatoma cell line with stable integration of human CYP1A1 (a P450 enzyme) promoter and enhancer sequences fused to the firefly luciferase reporter gene and the endogenous expression of the Ah receptor, which is a transcription factor that induces the expression of the CYP1A1 protein involved in drug metabolism. Therefore, the first nucleic acid (reporter plasmid) is within the chromosome and the second nucleic acid (transcription factor) is within the chromosome and endogenous to the cell. The cell line is treated with inducers of the CYP1A1 gene and the expression of the reporter gene indicates the regulation of the CYP1A1 gene by the inducer and the Ah receptor. Thus, Quattrochi et al teach all that is recited in the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 9-11 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann et al (Journal of Clinical Investigation, (1998), volume 102,

issue 5, pages 1016-1023) in view of Iyers et al (European Journal of Cancer, 1998, volume 34, issue 10, pages 1493-1499) and Windmill et al (Mutation Research, (1997), volume 376, pages 153-160).

Claims 1-4, 9-11 and 14-19 have been described previously.

Lehmann et al (Journal of Clinical Investigation, (1998), volume 102, issue 5, pages 1016-1023) et al transient transfection of CV-1 kidney cells with human and mouse PXR (pregnane X receptor which is an orphan hormone receptor) expression plasmids and a reporter plasmid containing a CYP3A4 PXRE regulatory element and a reporter gene such as the enzyme CAT, treatment of the transfected cell with various compounds and detection of reporter gene expression as an indication of the effect of the interaction of the compound and PXR on the regulation of CYP3A4 gene expression (page 1017, left column, second full paragraph, lines 15-18; page 1019, right column, second paragraph, lines 11-18 bridging page 1020, lines 1-3; page 1020, lines 1-15). CYP3A4 is a P450 enzyme involved in drug metabolism. Lehmann et al do not teach the use of this system in additional cell types such as lung or liver or with other drug metabolizing enzymes.

Iyer et al teach the use of pharmacogenetics in screening drug toxicity that evaluate specific drug metabolizing enzymes including glutathione S-transferases, uridine diphosphate glucuronosyl-transferases, and cytochrome P450 enzymes (abstract, lines 5-8).

Windmill et al demonstrates that at the time of the invention it was known that a cytochrome P450 enzyme was expressed in "human liver, stomach, small and large

intestine, gall bladder, appendix, lung, kidney and adrenals" (page 156, left column, lines 11-19). They further demonstrate that CYP3A4 is the main P450 enzyme in the human small intestines and the liver (Page 156, right column, lines 4-7).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Lehmann et al to also use cells from the lung and the liver and to test other drug metabolism enzymes because Lehmann et al teach that it is within the skill of the art to use a cell to test compounds that will bind or activate an intracellular receptor and cause the expression of the reporter gene controlled by a regulatory element of a drug metabolism enzyme. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Lehmann et al and actually exemplified by Iyers et al and Windmill et al, of using cells from the lung or liver to test compounds that are involved in the regulation of the gene expression of drug metabolism enzymes such as a glutathione transferase or glucuronosyl transferase. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in using lung or kidney cells since it has been shown that drug metabolism enzyme genes are expressed in these tissues.

Claims 1-4, 7, 9-11 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann et al (Journal of Clinical Investigation, (1998), volume 102, issue 5, pages 1016-1023) in view of Pascussi et al (Molecular Pharmacology, (2000), volume 58, pages 361-372) and Foulkes et al (US 5,976,793).

Claims 1-4, 9-11 and 14-19 have been described previously. Claim 7 limits the invention of claim 1 to the enhancer or promoter being endogenous to the chromosome.

Lehmann et al has been described previously. Lehmann et al teaches the transfection of cells with the CYP3A4 reporter construct and the PXR expression vector, but does not teach transfection of cells that contain the CYP3A4 regulatory element in their chromosome.

Pascussi et al demonstrates that human liver cells treated with a compound such as dexamethasone induces PXR expression and induces CYP3A4, a P450 drug metabolism enzyme, expression in response to known PXR activators (abstract, page 362, right column, first full paragraph, lines 1-4, page 366, right column, first full paragraph, last 4 lines).

Foulkes et al demonstrate a reporter gene inserted downstream of an endogenous promoter in the chromosome of a cell that is used in an assay to determine if a molecule is able to transcriptionally modulate a gene of interest by contacting the test molecule with the modified cell (column 27, lines 19-55).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Lehmann et al et al to perform the transfections in primary cells such as human hepatocytes because these cells have been shown to endogenously express the P450 drug metabolism enzymes such as CYP3A4 and factors such as PXR that are involved in the regulation of P450 enzymes. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Lehmann et al and actually exemplified by Pascussi et al and Foulkes et al to use a cell that endogenously

expresses a drug metabolism enzyme of interest and insert a reporter gene downstream of the regulatory elements in order to see the level of regulation by the promoter or enhancer elements in a natural occurring situation. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in using a human hepatocyte since it has been shown that compounds induce the expression of PXR which then up-regulates the expression CYP3A4 in this cell type.

Claims 1-4, 8, 9-11 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann et al (Journal of Clinical Investigation, (1998), volume 102, issue 5, pages 1016-1023) in view of Boeke et al (US 5,840,579).

Claims 1-4, 9-11 and 14-19 have been described previously. Claim 8 limits the invention of claim 1 to the reporter gene being endogenous to the chromosome.

Lehmann et al has been described previously. Lehmann et al does not teach using cells with an endogenous reporter gene.

Boeke et al demonstrates a cell in which a promoter is operably linked to an endogenous reporter gene (column 7, lines 45-67 bridging column 8, lines 1-7).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Lehmann et al et al to use a cell that endogenously expresses a reporter gene. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Lehmann et al and actually exemplified by Boeke et al to use a cell that endogenously expresses a reporter gene to produce more consistent expression levels and therefore more reliable results in the detection of the reporter gene

expression. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in using an endogenous reporter gene since it has been shown that such a system yields reliable results.

Claims 1-4, 9-11 and 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann et al in view of Collins et al (US Patent 6,579,686).

Claims 1-4, 9-11 and 14-19 have been described previously. Claim 19 limits the invention of claim 20 to a high throughput method.

Lehmann et al has been described previously. Lehmann et al do not teach a high throughput method.

Collins et al demonstrate the transient transfection of CV-1 kidney cells in a 96-well plate format with a CAR (a receptor related to PXR) expression vector and CYP3A4-XREM-luciferase reporter construct, treatment of the cells with a compound, and measurement of luciferase activity, which is indicative of the compounds ability to alter the expression of CYP3A4 gene expression (column 3 lines 29-36, column 6 lines 46-67 bridging column 7 lines 1-2 and column 8 lines 35-52). The use of this high throughput method was well known at the time if this invention. It would have been obvious to one of ordinary skill in the art to modify the teachings of Lehmann et al to perform the transfections in a 96-well plate high throughput format. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Lehmann et al and actually exemplified by Collins et al of being able to screen more compounds and conditions in one experiment. Absent of any evidence to the contrary,

there would have been a reasonable expectation of success in using the 96-well plate format since it is known that the transfection of cells and the analysis of an assay can be performed in a 96-well plate.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-20 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of copending Application No. 10/222,679. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 150-172, 174-202 and 204-205 of copending Application No. 09/832,621. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed species in Application No. 09/832,621 anticipates the claimed genus in Application No. 10/642,322. The claims of both applications encompass a cell containing a first nucleic acid with a gene regulatory element and a reporter gene and a second nucleic acid encoding an intracellular receptor or transcription factor and a method of using the cell to evaluate compounds by contacting the compound with the cell and detecting the expression of the reporter gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-

2917. The examiner can normally be reached on Monday through Friday 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tara L Garvey
Examiner
Art Unit 1636

TLG

JAMES KETTER
PRIMARY EXAMINER